# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>ARDK/P28276PC | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/GB 03/03669 | International filing date *(day/month/year)*<br>21.08.2003 | Priority date *(day/month/year)*<br>23.08.2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>A61K38/08 | | |
| Applicant<br>VALORISATION-RECHERCHE, societe en commandite etal | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 23.03.2004 | 30.11.2004 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Böhmerova, E<br>Telephone No. +49 89 2399-7859 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/03669

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-27 as originally filed

**Claims, Numbers**

1-15 filed with telefax on 23.08.2004

**Drawings, Sheets**

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-6,13-15

   because:

   ☒ the said international application, or the said claims Nos. 1-6,13-15 relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-15 |
| | No: | Claims | - |
| Inventive step (IS) | Yes: | Claims | 1-15 |
| | No: | Claims | - |
| Industrial applicability (IA) | Yes: | Claims | 7-12 |
| | No: | Claims | - |

2. Citations and explanations

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

International application No. PCT/GB 03/03669

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 1-6, 13-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**Cited documents**

Reference is made to the following documents:

D1: WO-A-0023097

D2: WO-A-9822124

D3: WO-A-0067770

D4: WO-A-0009537

D5: BROGLIO FABIO ET AL: "Effects of acute hexarelin administration on cardiac performance in patients with coronary artery disease during by-pass surgery" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 448, no. 2-3, 19 July 2002 ), pages 193-200

D6: WALKER RICHARD F ET AL: "Effects of stimulated growth hormone secretion on age-related changes in plasma cholesterol and hepatic low density lipoprotein messenger RNA concentrations" MECHANISMS OF AGEING AND DEVELOPMENT, vol. 75, no. 3, 1994, pages 215-226

D7: MARLEAU S ET AL: "Effect of growth hormone releasing peptides (GHRPs) on monocyte/macrophage scavenger receptors (SR) B (CD36) expression and monocyte trafficking" INFLAMMATION RESEARCH, vol. 50, no. Supplement 3, September 2001, page S154

Unless indicated otherwise reference is made to the passages considered relevant in the search report.

D1 discloses the use of growth hormone (GH)-releasing compounds including hexarelin

for the treatment of familial hypercholesterolemia. D2 discloses the use of growth hormone releasing peptide (GHRP)-like compounds including hexarelin for the treatment or prevention of cardiac failure and related vascular dysfunction including myocardial infarction. D3 teaches the use of GHRP for the treatment of acute ischemic events such as myocardial infarction. D4 discloses peptides having GH releasing activity and the use thereof for decreasing the serum cholesterol and LDL and increasing the serum HDL. D5 discloses the positive effects of hexarelin administration on cardiac performance in patients with coronary artery diseases during by-pass surgery. D6 teaches that ageing is associated with a progressive increase in plasma cholesterol levels in rats. This increase is reduced by administration of GHRP. D7 teaches that hexarelin induces a decrease in CD36 expression in monocyte / macrophages (MO), leading to a reduced monocyte trafficking in response to exogenous oxLDL-elicited MO accumulation in the peritoneal cavity.

**Novelty**

The original claims have been restricted to atherosclerosis as the only condition to be treated or prevented by the GHRPs or derived peptidomimetics. Such disclosure is novel as none of the above cited documents teaches the activity of GHRPs in the treatment or prevention of atherosclerosis. Consequently, the subject-matter of amended claims 1-3, 7-9, 13-15 is considered to be novel under Art. 33(1) and (2) PCT. Novelty of the subject-matter of amended claims 4-6, 10-12 has been already acknowledged in the Written Opinion.

**Inventiveness**

Subject-matter of claims 1-3, 7-9, 13-15 is considered as involving an inventive step under Art. 33(1) and (3) PCT for the following reasons: The problem to be solved by those claims can be defined as to provide an agent for the treatment or prevention of atherosclerosis. The solution proposed by the application is the use of one or more GHRPs or derived peptidomimetics. Although the cited prior art teaches the use of GHRPs in the treatment and prevention of hypercholesterolemia and different cardiovascular diseases, none of the cited documents suggests the use thereof in the treatment or prevention of atherosclerosis.

The problem to be solved by claims 4-6, 10-12 is to provide an agent for increasing the

expression of genes involved in cellular cholesterol efflux. The solution as claimed is the use of one or more GHRPs. Figure 8 of the present application demonstrates that treatment with GHRPs increases the expression of genes involved in cellular cholesterol efflux (LXRalpha and ABCA1) in macrophages. None of the cited documents suggest that GHRPs can provide for such an activity. Consequently, the subject-matter of claims 4-6, 10-12 is considered to involve an inventive step under Article 33(1) and (3) PCT.

**Industrial applicability**

Subject-matter of independent claims 7-12 is considered to be industrially applicable under Art. 33(1) and (4) PCT.

For the assessment of the present claims 1-6, 8-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Claims**

1. A method of treatment or prophylaxis of atherosclerosis, which method comprises administration of one or more GHRPs to a patient in need of such treatment or prophylaxis.

2. A method as claimed in Claim 1, which comprises preventing the development of atherosclerotic plaques by administering one or more GHRPs to a patient at risk of developing such plaques, hypercholesterolemia or cardiovascular diseases.

3. A method as claimed in Claim 1, which comprises treating pre-existing atherosclerosis by administering one or more GHRPs to a patient who has atherosclerosis.

4. A method of increasing expression of genes involved in cellular cholesterol efflux, which method comprises administering one or more GHRPs to a patient who would benefit from increased expression of such genes.

5. A method as claimed in Claim 4, wherein the genes involved in cellular cholesterol efflux are those for nuclear receptor LXRα and/or ABCA1 transporter.

6. A method as claimed in any one of the preceding claims, wherein the one or more GHRPs are hexarelin (His-(D)-(Me)Trp-Ala-Trp-(D)-Phe-Lys-$NH_2$) or EP80317 (Haic-(D)-(Me)Trp-(D)-Lys-Trp-(D)-Phe-Lys-$NH_2$).

7. The use of one or more GHRPs for the manufacture of a medicament for the treatment or prophylaxis of atherosclerosis.

8. Use as claimed in Claim 7, wherein the medicament is for preventing the development of atherosclerotic plaques.

9. Use as claimed in Claim 7, wherein the medicament is for treating pre-existing atherosclerosis.

10. The use of one or more GHRPs for the manufacture of a medicament for increasing expression of genes involved in cellular cholesterol efflux in a patient who would benefit from increased expression of such genes.

11. Use as claimed in Claim 10, wherein the genes involved in cellular cholesterol efflux are those for nuclear receptor LXRα and/or ABCA1 transporter.

12. Use as claimed in any of Claims 7 to 11, wherein the one or more GHRPs are hexarelin (His-(D)-(Me)Trp-Ala-Trp-(D)-Phe-Lys-$NH_2$) or EP80317 (Haic-(D)-(Me)Trp-(D)-Lys-Trp-(D)-Phe-Lys-$NH_2$).

13. The use of growth hormone releasing peptides of Hexarelin family, of derived peptidomimetics and of CD36 ligands in the prevention and treatment of atherosclerosis.

14. The use of GHRP derivatives, of derived peptidomimetics, and of CD36 ligands which modulate the expression of scavenger receptor B (CD36) in the prevention of the development of atherosclerotic lesions.

15. The use of GHRP derivatives and of derived peptidomimetics which modulate the expression of the ATP-binding cassette ABCA1 transporter and scavenger receptor B (CD36) in the prevention of the development of atherosclerotic lesions.